REMARKS

Pursuant to the entry of the instant amendment, claims 1-14 are presently pending in the instant application. Herein, new claim 14 is presented, said claim including subject matter previously recited in and now cancelled from claim 7 from which claim 14 depends. Accordingly, Applicants respectfully submit that no new matter has been added. Applicants further submit that the present amendment should not be construed as a narrowing amendment presented for the purposes of patentability.

Pursuant to the Non-Final Office Action of August 22, 2007, all claims stand rejected as anticipated and/or obvious in view of the cited prior art. Applicants respectfully disagree and request reconsideration and withdrawal of the outstanding rejections in view of the following remarks:

Rejections under 35 U.S.C. § 102

Claims 1, 5, 7, and 8 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by Canning et al. (USPN 6,979,442). According to the Examiner, Canning et al. teach stabilized protein pharmaceutical compositions, for example a pharmaceutical composition of G-CSF or EPO, that includes a stabilizing buffer, such as tris-(hydroxymethyl)-aminomethane ("TRIS"), "present in a concentration ranging from about 0.005M to about 2 M (column 4, lines 28-31)", said composition having a pH "in the range from about 4.0 to about 8.0 (column 13, line 46 to column 14, line 45)". The Examiner thus concludes that the invention of the present claims is anticipated by the Canning disclosure.

Applicants respectfully disagree with the Examiner's characterization of the Canning disclosure as well as her conclusion of anticipation. On the issue of anticipation, it is well settled that a genus disclosure will not always anticipate a claim to a particular species within the genus. See M.P.E.P. § 2131.02, citing to *Ex parte A*, 17 USPQ2d 1716 (BPAI, 1990). When a particular compound, composition or combination is not specifically named, but instead it is necessary to, in hindsight, select portions of teachings within a reference and combine them (e.g., select

various substituents from a list of alternatives to arrive at a specific composition), anticipation can only be found if the class or classes of substituents are sufficiently limited or well delineated. In other words, only when one of ordinary skill in the art can "at once envisage" the specific combination within the generic formulation can the specific combination be deemed anticipated. To that end, one should look to the disclosed preferred embodiments to determine which compounds can be anticipated. *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

In this case, the Canning disclosure relates to a surprising discovery that proteins, in particular proteins useful in treating infections in mammals, can be stabilized by the addition of a stabilizing buffer, such as HEPES, TES and TRICINE. The Canning disclosure is particularly directed to stabilized G-CSF compositions, though other exemplary proteins include "activins, adhesion molecules, such as L-selectin, CD-18 and ICAM-1, chemokines, chemotactic factors, erythropoietin, growth factors, inhibins, insulin, interferons, such as alpha, beta and gamma; interleukins, such as interleukins 1-18, leptin, macrophage inflammatory proteins, macrophage migration inhibitory factor, macrophage stimulating protein, neurotrophins, neutrophil inhibitory factor, oncostatins, somatostatins, somatotrophins (all species), such as porcine, bovine or human, stem cell factors, tumor necrosis factors, thrombopoietins and cell associated and soluble receptors for all of the foregoing proteins and any and all other proteins which when administered to a mammal are capable of providing a beneficial or therapeutic result", as well as proteins "described in R&D Systems Catalogue" incorporated by reference (9:37-57). An exhaustive list of over 150 exemplary proteins is set forth in Table 1 (10:60-12:25).

In a similar fashion, while the Canning disclosure identifies HEPES, TES and TRICINE as particularly preferred and exemplified, other "stabilizing buffers" include "HEPES (N-2-Hydroxyethylpiperazine-N-2-ethanesulfonic acid), TES (N-Tris(hydroxymethyl) methyl-2 aminoethanesulfonic acid), and TRICINE (N-Tris(hydroxymethyl)methylglycine), cacodylic acid, Bis(2-hydroxyethyl)-imino-tris(hydroxymethyl)methane (BISTRIS), Piperazine N,N'bis-(2 ethane sulfonic acid) (PIPES), Imidazole and Tris(hydroxymethyl)aminomethane (TRIS)" (13:38-59) as well as the examples set forth in Table 2 (13:63-14:35).

It is readily apparent that the wide range of alternatives disclosed by Canning gives rise to a virtually unlimited number of possible combinations. However, the pending claims are directed to only one select species within this genus, namely an unexpectedly stable pharmaceutical formulation of erythropoietin stabilized with tris-(hydroxymethyl)-aminomethane, a formulation that excludes the amino acid and human serum albumin stabilizers that are conventional in the prior art EPO formulations. Neither of the components of the presently claimed pharmaceutical formulation is identified by Canning et al. as preferred or illustrated in any of the recited examples, much less identified as useful together. Accordingly, given the fact that EPO is listed among hundreds of possible proteins, thousands if you include the entire R&D Systems Catalogue, Applicants respectfully submit that selecting it alone for further consideration amounts to finding a needle in a haystack. Moreover, since tris-(hydroxymethyl)-aminomethane ("TRIS") is similarly listed among over 20 possible "stabilizing buffers", Applicants submit that the likelihood of arriving at a composition comprised of these two select components "would be the same as discovering the combination of a safe by the inspection of its dials". *Ex parte Garvey*, 41 USPQ 583 (POBA 1939); *Ex parte Starr*, 44, USPQ 545 (POBA 1938).

Thus, Applicants submit that one could arrive at the presently claimed combination only through a meticulous selection of substituents for which Canning provides no motivation or guidance. Accordingly, since one of ordinary skill in the art could not have "at once envisaged" the presently claimed combination of elements from the Canning disclosure, Applicants respectfully submit the generic teachings of Canning cannot anticipate the species presently claimed.

As to the specific concentration of tris-(hydroxymethyl)-aminomethane set forth in Applicants' claims 2 and 8 *et seq*., the Examiner (citing to column 4, lines 28-31) asserts that the Canning reference discloses a range of "0.005M [sic] to about 2 M". However, Applicants wish to point out that Canning et al. in fact disclose a range of **0.05M** to 2M, which corresponds to a range of 50 mM to 2000 mM. Conversely, Applicants' claims specify concentrations of 10 to 200 mM (claim 2) and 20 to 100 mM (claim 8), respectively. When a prior art reference discloses a range

which touches or overlaps a claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. See M.P.E.P. § 2131.03. In order to anticipate, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute anticipation under the statute." The question of what constitutes "sufficient specificity" is analogous to the inquiry of "clearly envisaging" discussed above. For example, if the claims are directed to a narrow range, and the reference teaches a broad range, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. In addition, when there is only a slight overlap between the reference's preferred range and the claimed range, that overlap may not be sufficient for anticipation.

In this case, while there is slight overlap between Applicants' upper permitted range (200 mM) and Canning's lower permitted range (50 mM), it is telling that the Canning examples, utilizing buffer concentrations of 0.1M, 1M and 2M (i.e., 100 mM, 1000 mM, 2000 mM), conclusively demonstrate that the lower concentration (e.g., 0.1M) is markedly less stable and therefore less preferred (see Figures 1, 2). Applicants' narrowly claimed concentrations of 10 to 200 mM (claim 2) and 20 to 100 mM (claim 8) not only fall below this "less preferred" mark but also encompass only about 8% and 3%, respectively, of the breadth of Canning's disclosed range. Thus, Applicants submit that the Canning reference fails to disclose the claimed concentration ranges with sufficient specificity to anticipate the invention of claims 2 and 8. Furthermore, given that inclusion in an EPO formulation of tris-(hydroxymethyl)-aminomethane stabilizer at such concentrations give rise to a surprising reduction in protein aggregation, Applicants submit the Canning reference also fails to render obvious the invention of claims 2 and 8.

As to the pH ranges set forth in Applicants' claims 7 and 14, the Examiner (citing to column 13, line 46 to column 14, line 45) asserts that "Canning et al. teach that the pH of the stabilized protein composition can be in the range from about 4.0 to 8.0." However, upon further review of the relevant disclosure, particularly 5:5-25 and 14:38-45, Applicants note Canning et al. distinguish between "stabilized protein compositions", which indeed may be maintained at a pH "of about 4.0 to about 7.5, preferably 4.0" and "pharmaceutically acceptable dosage forms of

a stabilized protein composition", which, of necessity, must be maintained at "physiological pH", defined as generally within the range of 6.5 and 8.0, more preferably about 7.5. Accordingly, in the context of "stable ***pharmaceutical*** formulations" as presently claimed, Applicants respectfully submit that the Canning disclosure is limited to pH ranges of 6.5 and 8.0, more preferably about 7.5, a range that fails to suggest the narrowly claimed pH ranges of 5.9 to 6.8 (claim 7), more preferably 6.2 to 6.6 (claim 14), with a specificity sufficient to constitute anticipation thereof. Furthermore, as noted in the instant specification, particularly at the paragraph spanning pages 3 and 4, while TRIS is well recognized as a buffer for pharmaceutical formulations, it is typically used in the pH range between 7 and 9 and shows little to no buffering ability at a pH between 5.9 and 6.8. Accordingly, even assuming, *arguendo*, that one skilled in the art opted to select TRIS as the "stabilizing buffer" in the context of a Canning composition, he most certainly would not have been motivated to do so at a pH of less than 7, much less a pH ranging between 5.9 to 6.8, more preferably between 6.2 to 6.6, as required by the invention of pending claims 7 and 14, respectively. In fact, the surprising ability of tris-(hydroxymethyl)-aminomethane to act as a pharmaceutical *stabilizer* (in contrast to a *buffer*) for EPO at the recited pH constitutes one of the unexpected discoveries that is central to the present invention. For these additional reasons, Applicants submit the Canning reference fails to anticipate or render obvious the invention of claims 7 and 14.

In sum, Applicants respectfully submit that since the Canning reference fails to disclose or suggest the each and every element of the pending claims with the requisite specificity and particularity, it cannot anticipate the presently claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the rejection of the claims 1, 5, 7, and 8 under 35 U.S.C. § 102.

Rejections under 35 U.S.C. § 103

Sharma & Naeff:

Claims 2-4 and 6 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Sharma et al. (USPA 2003/0148938) and Naeff et al. (USPN 6,645,522). According to the Examiner, while Canning et

al. fail to teach a pharmaceutical formulation comprising EPO, tris-(hydroxymethyl)-aminomethane, together with a sodium phosphate buffer and NaCl, the Sharma reference cures this deficiency by teaching the inclusion in pharmaceutical formulations of sodium phosphate buffers, for example in a range from about 10 mM to about 30 mM, and NaCl, for example as an ionic toxicity agent at a concentration of about 75 mM to about 100 mM. The Examiner cites to Naeff for specifically teaching the use of sodium phosphate buffering agents, namely sodium hydrogen phosphate dehydrate and disodium hydrogen phosphate dehydrate, in EPO formulations. The Examiner thus concludes that it would have been obvious to include the additional components taught by Sharma and Naeff in the Canning EPO pharmaceutical formulation to arrive at the invention presently claimed.

Applicants respectfully disagree with the Examiner's characterization of the prior art as well as her conclusion of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See M.P.E.P. § 2142, 2143. Moreover, in considering the issue of obviousness and the degree to which combined teachings of the references would have suggested to one of ordinary skill in the art, all teachings in the prior art must be considered to the extent that they are in analogous arts.

On the issue of motivation, it is important to note that the burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972,

973 (Bd. Pat. App. & Inter. 1985). Merely suggesting that a reference could be physically modified does not render the resulting modification "obvious" unless the prior art also suggests the desirability of the modification. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

In this case, Applicants respectfully submit that neither Sharma nor Naeff cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the invention of claims 2-4 and 6. Specifically, neither reference provides a motivation to combine EPO with a tris-(hydroxymethyl)-aminomethane stabilizer in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. Furthermore, regarding the proposed combination of Naeff or Sharma and Canning, while Naeff or Sharma may arguably suggest the exchange of Canning's TRIS stabilizing buffer for the sodium phosphate buffer systems disclosed by Naeff and Sharma, there is certainly no suggestion to modify the Canning composition to formulate a protein composition with both TRIS and sodium phosphate together as pending claim 2 requires.

Thus, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 2-4 and 6 under 35 U.S.C. § 103.

Woog:

Claims 9-11 and 13 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Woog et al. (USPN 4,992,419). According to the Examiner, while Canning et al. fail to teach a pharmaceutical formulation comprising EPO, tris-(hydroxymethyl)-aminomethane, together with a non-ionic detergent, the Woog reference cures this deficiency by teaching that adhesion of EPO to ampoule walls and syringes can be reduced by the addition of small amounts of detergents, for example non-ionic wetting agents such as Tween 20, Tween 80, and sorbitan trioletate at concentrations ranging from 0.05 to 5 g/l, more particularly 0.1 to 0.5 g/l. The Examiner thus concludes that it would have

been obvious to include the additional component disclosed by Woog in the Canning EPO pharmaceutical formulation to arrive at the invention presently claimed.

Applicants respectfully disagree with the Examiner's characterization of the prior art as well as her conclusion of obviousness. As above, Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness because, like Sharma and Naeff, Woog et al. fail to cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the invention of claims 9-11 and 13. Specifically, the Woog reference fails to provide a motivation to combine EPO with a tris-(hydroxymethyl)-aminomethane stabilizer in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. In fact, Woog et al. specifically teach away from such a combination by disclosing an EPO formulation that expressly requires amino acids for stabilization. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claims 9-11 and 13 under 35 U.S.C. § 103.

Konings:

Claim 12 stands rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Canning et al. (USPN 6,979,442) as applied to claim 1, further in view of Konings et al. (USPN 5,376,632). According to the Examiner, while Canning et al. fail to teach a pharmaceutical formulation comprising EPO, tris-(hydroxymethyl)-aminomethane, together with EDTA in an amount ranging from 0.1 to 0.5 mM, the Konings reference cures this deficiency by teaching methods for stabilizing EPO in an aqueous solution, more particularly methods for avoiding the heavy metal catalyzed degradation of EPO through the inclusion of suitable complexing agents, such as calcium chloride or EDTA, for example at a concentration ranging from 0.2 to 2 g/l (i.e., 0.1 to 0.5 mM). The Examiner thus concludes that it would have been obvious to include the additional components disclosed by Konings in the Canning EPO pharmaceutical formulation to arrive at the invention presently claimed.

Applicants respectfully disagree with the Examiner's characterization of the prior art as well as her conclusion of obviousness. As above, Applicants respectfully submit that the Examiner has failed to set forth a *prima facie* case of obviousness because, like Sharma, Naeff, and Woog, Konings et al. fail to cure the deficiencies of the Canning reference noted in the context of pending claim 1, much less provide the requisite motivation or suggestion for the invention of claim 12. Specifically, the Konings reference fails to provide a motivation to combine EPO with a tris-(hydroxymethyl)-aminomethane stabilizer in the absence of amino acids and human serum albumin to arrive at the surprising stable pharmaceutical formulation of the pending claims. In fact, Woog et al. specifically teach away from such a combination by disclosing an EPO formulation that expressly requires modified beta or gamma cyclodextrin for stabilization. Accordingly, Applicants respectfully submit that the cited references, alone or in combination, fail to render obvious the invention of the pending claims. Thus, Applicants request reconsideration and withdrawal of the rejection of claim 12 under 35 U.S.C. § 103.

In sum, Applicants submit that the invention of the pending claims is neither anticipated nor rendered obvious by the prior art of record. Accordingly, Applicants submit that pending claims 1-14 are in condition for allowance and respectfully petition for an early indication of such.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **November 22, 2007**. Accordingly, Applicant submits that this response is timely and that no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to the undersigned's Deposit Account No. **50-2101**.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: November 14, 2007

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